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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/697,995	10/30/2003	Dorothea Reilly	11669.195USU1	7395

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EXAMINER	
CROWDER, CHUN	
ART UNIT	PAPER NUMBER
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/697,995	REILLY ET AL.	
	Examiner	Art Unit	
	Chun Crowder	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/27/2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55,57-101 and 103-114* is/are pending in the application.

4a) Of the above claim(s) *86 and 100* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55, 57-85, 87-99, 101, and 103-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/14/06 and 10/27/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment to the claims, filed 10/27/2006, is acknowledged.

Claims 1-54, 56, 102 and 115-120 have been canceled.
Claims 55, 57-59, 66-72, 84, 88, 89, 93-95, 105-109, and 113 have been amended.

Claims 55, 57-101, 103-114 are pending.

Claims 86 and 100 have been withdrawn from consideration, under 37 C.F.R. 1.142(b), as being drawn to nonelected inventions.

Claims 55, 57-85, 87-99, 101, and 103-114 are currently under consideration as they read on the originally elected invention of a polynucleotide encoding an antibody IgG1, a vector, *E.Coli* host cells, DsbA, and the heavy and light chains are encoded by a single polynucleotide and a method of producing the antibody.

2. This Office Action will be in response to applicant's arguments, filed 10/27/2006.

The rejections of record can be found in the previous Office Action, mailed 06/30/2006.

The text of those Sections of Title 35 U.S.C. not included in this Action can be found in a prior Action.

3. Applicant's IDSs, filed 07/14/2006 and 10/27/2006, are acknowledged and have been considered.

4. Claims 63, 64 and 99 are objected to because of the following informalities. The claims recite "DsbA, DsbC...". It is suggested that applicant amend the claims to recite the full name of the "Dsb" for reasons of record.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that the term "Dsb" is an acronym for the phrase disulfide bond formation and is an art-recognized term; therefore, applicant is not required to provide a full name of the term.

This is not found persuasive for following reasons:

An abbreviation can indicate a number of entities. For example, in searching the Examiner's Automated Search Tool (EAST) site, the abbreviation "Dsb" indicated a number of entities not related to the claimed molecule.

Applicant is once again suggested to amend the claims to recite the full name of the "Dsb".

5. Claims 55, 57-85, 87-99, 101, and 103-114 are rejected under **35 U.S.C. 112, first paragraph,** as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record.

The following *written description* rejection is set forth herein.

Applicant's arguments have been fully considered but have not been found persuasive.

Applicant argues that compliance with the written description requirement does not require an applicant to describe exactly the subject matter claimed; rather, the description must clearly allow a person of ordinary skill in the art to recognize that he or she invented what is claimed. Further, applicant argues that the recitation of known structure is not required to satisfy written description; the specification is replete with examples of heavy chain variant regions having one or more cysteine residues replaced with serine residues. Furthermore, applicant asserts that the art is replete with a large number of antibodies which have been cloned and the nucleotide sequences encoding both the heavy and light chains obtained. The cDNA sequences of many antibodies, antibody parts (i.e., heavy chain, light chain, CDR regions, Fc regions, constant regions, variable regions, etc.), as well as the genomic nucleotide sequences, are publicly available. The claimed invention is not dependent upon the specificity of the antigen binding region, Just as a polynucleotide sequence comprising a cDNA can be expressed in a wide variety of host cells, or expressed from a wide variety of expression vectors, a heavy chain having a variant heavy chain hinge region can be a part of any number of antibodies, regardless of the antigen binding specificity of the variable regions. Therefore, applicant argues that one of skill in the art can readily modify nucleic acids disclosed in the specification to encode other antibodies and the sequences of antibodies and antibody hinge regions can be readily determined by those of skill in the art.

This is not found persuasive for following reasons:

Contrary to applicant's assertion, the specification as filed does not disclose a sufficient number of species to support the "polynucleotide" as broadly encompassed by the claimed invention.

The instant claims are drawn to a polynucleotide encoding an antibody, a vector, a host cells and a method of producing an antibody.

Such "polynucleotide encoding an antibody" does not meet the written description provision of 35 U.S.C. 112, first paragraph. There is insufficient guidance and direction as to the written description of theses "polynucleotide encoding an antibody" as broadly encompassed by the claimed invention.

It is noted that "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); and there is a lack of written descriptive support for an antibody defined by its binding affinity to an antigen that itself was not adequately described. See MPEP 2163.

Here, the instant specification appears to describe the written description of the cDNAs corresponding to the particular antibodies (e.g. anti-tissue factor antibody and anti-VEGF antibody. See Examples on pages 57-67 of the instant specification). Thus, applicant has disclosed only a limited species of the "polynucleotide encoding an antibody", namely cDNAs encoding specific antibodies. The claimed "polynucleotide encoding an antibody" is defined as any nucleic acid include DNA and RNA, modified nucleotides, or bases, and their analogs or any substrate that can be incorporated into a polymer by DNA or RNA polymerase (see page 16 of the instant specification); as such the instant specification does not provide disclosure of relevant, identifying characteristics of the "polynucleotide encoding an antibody".

Further, the claimed polynucleotide would encompass genes or continuous or discontinuous regions of nucleic acids encoding an antibody. The claimed products may also contain additional coding and non-coding regions and, in turn, encompass the "gene". In addition, the invention could embrace any substitution, insertion or deletion change of nucleotides throughout the entire stretch of the polynucleotide encoding any antibody that has any antigen specificity.

It is well known that antibody diversity is critical and evident for a proper immune response, including making antibodies of interest. During B cell differentiation, antibody diversity is generated in the heavy and light chains of the immunoglobulin by mechanisms including multiple germ line variable (V) genes, recombination of V gene segments with joining (J) gene segments (V-J recombination) and recombination of V gene segments with D gene segments and J gene segments (V-D-J recombination) as well as recombinational inaccuracies. Furthermore, somatic point mutations that occur during the lifetime of the individual, immunized individual (e.g. immunized mouse for hybridomas) or a cell line also lead to antibody diversity. Thus, a huge number of different antibody genes coding for antibodies with exquisite specificity can be generated. The total potential immunoglobulin repertoire exceeds 10^{11}.

Therefore, given the well known polymorphism of immunoglobulins/antibodies; applicant was not in possession of the vast repertoire of "a polynucleotide encoding the antibody".

Therefore, the claims fail to comply with the 35 U.S.C. 112, first paragraph, written description requirement.

The rejections of record are maintained for the reasons of record, as they apply to the amended claims. The rejections of record are incorporated by reference herein as if reiterated in full.

6. Claims 55, 57, and 58 are rejected under **35 U.S.C. 102(b)** as being anticipated by Gillies et al. (Human Antibody Hybridomas. 1990 1;1:47-54. Cited on IDS filed 05/02/2006) and Davis et al. (The EMBO Journal 1989. 8;9:2519-2526. Reference cited on IDS filed 06/25/2004) for reasons of record.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Gillies et al. describes a heavy chain with cysteines replaced with serine that formed an antibody HL fragment and not an H2L2; Davis et al. describes mutations at Cys residues at position 337 (CH2), 414 (CH3), and 575 (tail) of IgM molecule involved in forming pentamers or hexamers of the IgM molecule and does not describe a heavy chain variant comprising a heavy chain hinge region that does not form inter-heavy chain disulfide linkages.

This is not found convincing for following reasons:

Contrary to applicant's reliance on certain examples of the prior art, the examiner recognizes that a prior art reference must be considered in its entirety. See MPEP 2141.02.

Here, Gillies et al. clearly teach an isolated polynucleotide encoding an intact antibody comprising a variant heavy chain wherein the variant heavy chain comprises a hinge region which does not form inter-heavy chin disulfide linkages because the heavy chain hinge region carries mutations of the two cysteine residues (see Materials and methods on pages 48-49 and Results on pages 50-52).

In this case, Davis et al. teach that there are four cysteines available for intermolecular disulfide bonding, at position 136, 337, 414, and 575; cysteine in position 136 of IgM is assumed to form disulfide bond with the light chain, where μ chain are joined by inter chain disulfide bonds via cysteines at position 337, 414, and 575 (see entire document, particularly Introduction on page 2519). Further, Davis et al. teach methods of making IgM variant by replacing cysteine residues responsible in forming inter-heavy chain disulfide bonds at position 337, 414, and 575 with serine using isolated polynucleotide encoding μ gene (see Material and methods on page 2526). Applicant's arguments have not distinguished the difference between the teachings of Davis et al. and the claimed invention.

Therefore, the reference teachings anticipate the claimed invention.

The rejections of record are maintained for the reasons of record, as they apply to the amended claim. The rejections of record are incorporated by reference herein as if reiterated in full.

7. Claims 55, 57-85, 87-99, 101, 103-114 are rejected under **35 U.S.C. 102(e)** as being anticipated by Simmons et al. (US Patent Application 2005/0170464) for reasons of record.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant argues that Simmons discloses substitution of any cysteines not involved in maintaining proper conformation of the antibody. There is no teaching and suggestion in Simmons that every cysteine can therefore be substituted. Simmons et al. fail to disclose a heavy chain that comprises a variant heavy chain hinge region.

This is not found persuasive for following reasons:

Contrary to applicant's assertion that Simmons et al. fail to teach each and every element of the claims, the examiner acknowledges that a generic chemical formula will anticipate a claimed species covered by the formula when the species can be "at once envisaged" from the formula; If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. See MPEP 2131.02.

Here, given that Simmons et al. specifically teach that the antibodies or immunocojugates can be variants with amino acid substitutions in the Fc regions and any cysteine residue may be substituted with serine to improve the oxidative stability and prevent aberrant crosslinking (e.g. see pages 12-15) and the limited number of cysteine residues in an antibody (see discussion above in Section 6), one skill artisan would immediately envisage that Simmons et al. taught the amino acid substitution from cysteine to serine in the Fc region including the those cysteine residues in the hinge region that are responsible forming inter-heavy chain disulfide bonds.

Therefore, the reference teachings anticipate the claimed invention.

The rejections of record are maintained for the reasons of record, as they apply to the amended claim. The rejections of record are incorporated by reference herein as if reiterated in full.

8. Claims 55, 57-85, 87-99, 101, and 103-114 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies et al. (Human Antibody Hybridomas. 1990 1;1:47-54. Cited on IDS filed 05/02/2006) and Davis et al. (The EMBO Journal 1989. 8;9:2519-2526. Reference cited on IDS filed 06/25/2004) in view of Georgiou et al. (US Patent 5,264,365. Reference cited on IDS filed 10/20/2004) and Kurokawa et al. (The Journal of Biological Chemistry. 2001. 276;17:14393-14399) for reasons of record.

Applicant's arguments have been fully considered but have not been found convincing.

Applicant's arguments and the examiner's rebuttal regarding the teachings of Gillies et al. and Davis et al. are essentially the same as above in Section 6.

Further, applicant argues that Kurokawa is directed to NGF and enhancing formation of disulfide bonds rather than a situation where such bonds are not formed. Georgiou is directed to forming E. coli strains deficient in proteases. There is no teaching or suggestion in the references even when combined of a polynucleotide encoding an intact antibody comprising a variant heavy chain as claimed. Moreover, applicant argues that there is no motivation to combine these references. Davis is concerned with understanding the linkage of antibodies to form an IgM subunit and does not discuss hinge region inter-heavy chain disulfide bonds or production of antibodies in cells. Gillies et al. is concerned with the interaction of the effector function and antigen binding hnction of antibodies and not with increasing intact antibody production in cells. Kurokawa is directed to enhancing disulfide bond formation. Georgiou is directed to E. coli cells deficient in proteases. Thus one of skill in the art would not be motivated to combine these references to achieve the claimed methods or polynucleotides.

This is not found persuasive for following reasons:

In response to applicant's arguments against the references individually, one cannot show non-obviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

It is noted that in considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom In re Preda, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). See MPEP 2144.01.

Furthermore, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY); and In re Burckel 201 USPQ 67 (CCPA). In re Burckel is cited in MPEP 716.02.

Regarding applicant's argument that Kurokawa et al. is directed to enhancing the formation of disulfide bonds rather than a situation where such bonds are not formed, it is noted that Kurokawa et al. teach that DsbA is a periplasmic enzyme that can act on nascent polypeptide chains in the formation of disulfide bonds during their protein foldings; as such the teachings of kurokawa et al. are not contradict to the claimed invention.

Here, given the teachings of Gillies et al. and Davis et al. regarding methods of making antibody variant incapable of forming inter-heavy chain disulfide linkage, and the teachings of Georgiou et al. and Kurokawa et al. providing methods of making antibody using E. Coli strains with Dsb proteins and deficient in proteases, the ordinary artisan at the time the invention was made would have had a reasonable expectation of success of producing antibody variant incapable of inter-heavy chain disulfide linkage formation using E. Coli strains with Dsb proteins and deficient in proteases.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

The rejections of record are maintained for the reasons of record, as they apply to the amended claim. The rejections of record are incorporated by reference herein as if reiterated in full.

9. Upon further consideration as well as applicant's amendments, the previous rejections under **35 U.S.C. 112, second paragraph** against claims 55, 58-85, and 103-114 and **35 U.S.C. 102(b)** against claims 59, 65-86, and 104 have been withdrawn.

10. Conclusion: no claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chun Crowder whose telephone number is (571) 272-8142. The examiner can normally be reached Monday through Friday from 8:30 am to 5:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Chun Crowder, Ph.D.
Patent Examiner
December 27, 2006

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TC-1600
12/28/06